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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
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10/578,955

05/10/2006

Robert K. Evans

21575P

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210

7590

06/28/2010

MERCK

P O BOX 2000

RAHWAY, NJ 07065-0907

EXAMINER

CHEN, STACY BROWN

ART UNIT

PAPER NUMBER

1648

MAIL DATE

DELIVERY MODE

06/28/2010

PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No. 10/578,955	Applicant(s) EVANS ET AL.	
	Examiner Stacy B. Chen	Art Unit 1648	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

- 1) ☒ Responsive to communication(s) filed on 19 May 2010.
- 2a) ☐ This action is **FINAL**. 2b) ☒ This action is non-final.
- 3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

- 4) ☒ Claim(s) 1-10,21-32 and 37-42 is/are pending in the application.
- 4a) Of the above claim(s) _____ is/are withdrawn from consideration.
- 5) ☐ Claim(s) _____ is/are allowed.
- 6) ☒ Claim(s) 1-10,21-32 and 37-42 is/are rejected.
- 7) ☐ Claim(s) _____ is/are objected to.
- 8) ☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

- 9) ☐ The specification is objected to by the Examiner.
- 10) ☒ The drawing(s) filed on 10 May 2006 is/are: a) ☒ accepted or b) ☐ objected to by the Examiner.
Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).
Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).
- 11) ☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

- 12) ☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
- a) ☐ All b) ☐ Some * c) ☐ None of:
1. ☐ Certified copies of the priority documents have been received.
 2. ☐ Certified copies of the priority documents have been received in Application No. _____.
 3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

- | | |
|--|---|
| 1) <input type="checkbox"/> Notice of References Cited (PTO-892) | 4) <input type="checkbox"/> Interview Summary (PTO-413) |
| 2) <input type="checkbox"/> Notice of Draftsperson's Patent Drawing Review (PTO-948) | Paper No(s)/Mail Date. _____ |
| 3) <input type="checkbox"/> Information Disclosure Statement(s) (PTO/SB/08) | 5) <input type="checkbox"/> Notice of Informal Patent Application |
| Paper No(s)/Mail Date _____ | 6) <input type="checkbox"/> Other: _____ |

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DETAILED ACTION

1. Applicant's amendment and remarks filed on May 19, 2010 are acknowledged and entered. Claims 1-10, 21-32 and newly presented claims 37-42 are pending and under examination.

Claims Summary

2. The claims are directed to a live adenovirus formulation comprising 0.25% to 0.6% (w/v), or 0.4% to 0.6% (w/v) chlorobutanol (CB), and a buffer within a pH range of 6.0 to 9.0, or more particularly, 6.4 to 7.4. Other components include various inhibitors of free radical oxidation, cryoprotectants, salts, divalent cations and non-ionic detergents. Also claimed is a vaccine vial comprising the formulation, and a method of preserving a live adenovirus formulation.

Claim Rejections - 35 USC § 103

3. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negated by the manner in which the invention was made.

Claims 1, 2, 9, 10, 21, 22, 29-32 and 37-42 are rejected under 35 U.S.C. 103(a) as being unpatentable over Gao *et al.* (WO 01/40455 A2, "Gao") in view of Taub *et al.* (*J. Amer. Pharm. Assoc.*, 1943, "Taub"). The claims are summarized above. Gao discloses live, recombinant adenovirus vectors for pharmaceutical use comprising a preservative, such as chlorobutanol (see page 19, first paragraph), and a buffer, such as PBS (page 18, lines 21-26). The adenovirus

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concentration taught by Gao is in the range of 10^{10} to 10^{18} for an adult human having a weight of about 80 Kg (see page 19, fourth paragraph).

Gao fails to teach the specific range of CB concentration. However, it would have been well within the ability of the ordinary artisan to determine which concentration of CB would have been appropriate for preserving the live adenovirus vectors. Given Gao's suggestion to use CB, the ordinary artisan would have then performed routine tests to determine the concentration of CB that can preserve the live viruses without compromising the integrity of the viruses.

Gao suggests the use of a buffer, but does not specifically teach a composition buffer within a pH range of 6.0 to 9.0, or more particularly, 6.4 to 7.4. However, it would have been well within the ability of the ordinary artisan to determine a suitable buffer and pH for the adenovirus/preservative composition. Given Gao's suggestion to use a buffer, which is also a standard practice in the art for stabilization purposes, the ordinary artisan would have then determined the appropriate pH for the composition without compromising the integrity of the preserved viruses. In view of Taub's teachings regarding the stability of CB at 0.5% in buffered solutions of not more than pH 7, one would have had a reasonable expectation of success.

Gao does not specifically teach that the formulation of live adenovirus contains CB in the amount of a lowest effective concentration of CB up to the solubility limit of CB for the formulation. However, Gao teaches that CB is used as a preservative in a live, recombinant adenovirus composition for administration. It would have been obvious to one of ordinary skill in the art and well within the ability of that individual to use an amount of CB that is effective for the purpose of preservation without exceeding the solubility limit for the formulation.

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Gao does not specifically teach the use of a multi-dose or single dose vial, however it would have been obvious to use a vial to store the contents of the formulation in order to contain and protect the formulation for delivery, storage and subsequent use. Gao discloses that the formulation of live, recombinant adenovirus can be administered using any suitable route, such as intravenous, intramuscular, etc. (see page 19, second paragraph). If one were to administer Gao's composition using a needle, then the formulation would necessarily come from a vial of some sort. As for the multi-dose or single dose vial, it would have been obvious and well within the ability of the ordinary artisan to package the contents of the vials according to the desired use. Gao teaches that the dose may be repeated as desired (see page 19, fourth paragraph). Therefore, the claimed embodiments would have been obvious at the time the invention was made.

Applicant's arguments have been carefully considered but fail to persuade. Applicant's substantive arguments are primarily directed to the following:

- Applicant argues that Gao does not teach any buffer having a pH within a range of 6.0 to about 9.0, or more particularly, 6.4 to 7.4. Applicant asserts that the art teaches that CB is not stable in buffered solutions greater than pH 6, see Taub *et al.* (*J. Amer. Pharm. Assoc.*, 1943) and Patwa *et al.*, (*J. Amer. Pharm. Assoc.*, 1943). Applicant also points to Akers (*Pharm. Technol.*, 1984) which discloses that CB is not effective as a preservative at a pH of 5 or greater. Applicant concludes that these teaching would lead one of ordinary skill in the art to avoid a pH in the range of 5-6.
- In response to Applicant's argument, the Office does not agree with Applicant's conclusion regarding the range of pH. Taub and Patwa teach that a pH of 6 is

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- acceptable, but that a pH higher than 6 is not. Akers teaches that a pH of 5-6 is not effective as a preservative. Given that two of the three references teach that a pH of 6 is acceptable, and the claims encompass a pH of 6.0, one of ordinary skill in the art would have had a reasonable expectation of success that a pH of 6.0 would have worked.
- Further, note also that Taub teaches that 0.5% CB solutions were stable in buffered solutions with a pH not above 7 (see page 30, conclusion 2). That solutions comprising CB and buffered at a pH not above 7 were found stable, is further evidence that it would have been well within the ability of the ordinary artisan to select an optimal pH for Gao's composition.
 - Applicant argues that the specification provides unexpected results relative to the prior art. For example, Table 7 shows that CB buffered at pH 7.4 (A195 buffer) provided effective antimicrobial activity and passed USP criteria and EP criteria B. Applicant argues that these results, compared with the prior art's teachings about CB buffered solutions being effective between 3-6, show that the claimed invention provides unexpected results. Applicant also argues that unexpected antimicrobial activity at pH 6.0, 6.8 and 7.4 are generally applicable to any adenovirus formulation within the claimed pH range.
 - In response to Applicant's argument, the Office could not locate the data for the unexpected antimicrobial activity at pH 6.0 and 7.4. Regardless, as stated above, Taub teaches that 0.5% CB solutions were stable in buffered solutions with a pH not above 7 (see page 30, conclusion 2). That solutions comprising CB and buffered at a

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pH not above 7 were found stable, is further evidence that it would have been well within the ability of the ordinary artisan to select an optimal pH for Gao's composition. Therefore, the rejection is maintained for reasons of record and in view of the above discussion.

4. Claims 3-8 and 23-28 are rejected under 35 U.S.C. 103(a) as being unpatentable over Gao *et al.* (WO 01/40455 A2, "Gao") and Taub *et al.* (*J. Amer. Pharm. Assoc.*, 1943) and Patwa *et al.*, (*J. Amer. Pharm. Assoc.*, 1943) as applied to claims 1 and 21 above, and further in view of Evans *et al.* (WO 01/66137 A1, "Evans"). Applicant's arguments have been addressed above.

Conclusion

5. No claim is allowed. In view of the new grounds of rejection, this Office action is made non-final.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see <http://pair-direct.uspto.gov>. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

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Any inquiry concerning this communication or earlier communications from the examiner should be directed to Stacy B. Chen whose telephone number is 571-272-0896. The examiner can normally be reached on M-F (7:00-4:30), alternate Fridays off,. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Jeffrey Stucker can be reached on 571-272-0911. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

/Stacy B Chen/
Primary Examiner, Art Unit 1648